Oscillations of Conduction, Action Potential Duration, and Refractoriness
A Mechanism for Spontaneous Termination of Reentrant Tachycardias

Lawrence H. Frame, MD, and Michael B. Simson, MD

The mechanism of cycle length oscillation and its role in spontaneous termination of reentry was studied in an in vitro preparation of canine atrial tissue surrounding the tricuspid orifice. Reentry occurred around a fixed path with incomplete recovery of excitability. Among 18 experiments, there was complete concordance between the occurrence of spontaneous cycle length oscillation and spontaneous terminations; both were observed in 10 experiments and neither in the other eight \((p<0.001\). Local changes in conduction during oscillations resulted from the dependence of both conduction velocity and action potential duration on the preceding local diastolic interval. Interval-dependent changes in action potential duration contributed to the oscillation by altering the next diastolic interval. Because of changes in action potential duration, changes in cycle length were poorly correlated with changes in diastolic interval and, therefore, with local conduction velocity. Complex oscillations resulted from variations in conduction time at multiple sites in the circuit. Oscillations caused most spontaneous terminations. The critical event was an exceptionally long diastolic interval preceding the next-to-last cycle that accelerated local conduction (which tended to shorten the last cycle) and prolonged action potential duration and refractoriness at the site of block. Ninety-two of 99 recordings of spontaneous termination showed evidence of oscillation of conduction and refractoriness causing block. \((Circulation 1988;78:1277-1287)\)

Spontaneous termination of reentrant tachycardias is common, but the mechanisms of termination and the properties of the circuit that contribute to those events are not generally known. One mechanism is the occurrence of spontaneous oscillations of cycle length that lead to termination. Simson et al\(^1\) described this mechanism in a canine model of atrioventricular tachycardia with an accessory bypass tract. They demonstrated that C1-dependent changes in conduction through the atrioventricular node were responsible for the cycle length oscillations and determined whether the tachycardia was stable or unstable. The stable tachycardias exhibited damped oscillations when perturbed. Unstable tachycardias exhibited spontaneous undamped cycle length oscillations that led to tachycardia termination when a sufficiently short cycle was reached. The oscillations in that model were always regular alternations of long and short cycles.

In this study, we demonstrate the mechanism of more complex cycle length oscillations and their role in spontaneous termination of tachycardia in a model of reentry around a fixed pathway in vitro. This preparation involves circus movement through incompletely recovered atrial tissue surrounding the tricuspid valve orifice and allows detailed observations about activation and conduction in all parts of the reentrant pathway. Our results suggest that both interval-dependent changes in conduction velocity and in the duration of action potentials and refractoriness contribute to the observed oscillations. Furthermore, variation in conduction velocity at multiple sites in the circuit produce complex irregular oscillations that can lead to conduction block and termination of reentry.

Materials and Methods

Eighteen healthy mongrel dogs weighing 15–20 kg were anesthetized with pentobarbital 30 mg/kg i.v. The heart was rapidly excised and immersed for
further dissection in cold Tyrode's solution equilibrated with 95% O₂-5% CO₂. The tricuspid ring preparation containing right atrial tissue was dissected and mounted, endocardium upward, in a special tissue bath as previously described.²

The Tyrode's solution contained (mM) NaCl 125, NaHCO₃ 24, NaH₂PO₄ 1.8, MgCl₂ 0.5, CaCl₂ 1.8, dextrose 5.5, and KCl 4.0. Solutions were continuously bubbled with 95% O₂-5% CO₂ before entering the tissue chamber and also at multiple sites around the circular chamber. The temperature of the chamber was maintained at 33–34°C. Acetylcholine and norepinephrine were added to the superfusate in some of the experiments. They were generally added at concentrations of 10⁻⁶ M when poor conduction or block developed in one part of the ring.² These agents were present throughout the experiment in two cases (one stable and one unstable tachycardia). The agents were not used at all in eight tachycardias (five stable and three unstable tachycardias). They were added during the course of the experiment in seven others (one stable and six unstable tachycardias). In this latter group, the agents decreased the tachycardia cycle length by 42 ± 28 msec and tended to decrease the amplitude of spontaneous cycle length oscillations.

Extracellular bipolar electrograms were recorded with pairs of Teflon-coated silver wire electrodes with an interpole distance of less than 0.5 mm. Ten recording electrode pairs were equally spaced in a circle around the tricuspid ring preparation. The interelectrode distance was 7–8 mm. Electrograms were amplified with a band width of 50–500 Hz. Activation was marked at the rapid zero crossing for biphasic electrograms or the peak of the largest deflection for monophasic or triphasic electrograms. Measurements are estimated to be accurate within 2 msec. Pacing stimuli 1 msec in duration and twice diastolic threshold current were delivered through separate bipolar silver wire electrodes located between the extracellular recording electrodes. Tachycardias were induced by single premature stimuli after a train of stimuli at a basic drive cycle length or by rapid pacing.

Transmembrane potentials were recorded with glass microelectrodes with tip resistances of 8–20 MΩ with a KS 700 amplifier (World Precision Instruments, New Haven, Connecticut). Intracellular and extracellular electrograms were recorded on chart paper at 100 or 250 mm/sec and on an FM tape recorder. The analysis of the mechanism of spontaneous termination of reentry includes only tachycardias that lasted at least 10 cycles.

Results
Correlation Between Spontaneous Termination and Cycle Length Oscillation

During 18 experiments in which reentry was induced, spontaneous terminations of reentry were observed multiple times in 10 experiments and were never observed in the other eight. Cycle length oscillations of more than 3 msec between consecutive cycles were observed during reentry (i.e., tachycardias were unstable) in each of the 10 experiments that demonstrated spontaneous termination. In contrast, cycle length oscillations were not observed (tachycardias were stable) in the other eight experiments in which spontaneous termination did not occur. This relation between cycle length oscillation and spontaneous termination was highly significant (p<0.001, χ² = 14.2 with Yates correction).

Damped Cycle Length Oscillations After Premature Stimuli in Stable Tachycardias

Although the stable tachycardias did not oscillate spontaneously, they did show damped cycle length oscillation after premature stimuli that reset the tachycardia. The example in Figure 1 shows variations in cycle length for several cycles after the stimulus that progressively diminished in amplitude until the tachycardia returned to its stable steady-state cycle length. The magnitude of cycle length oscillation varied at different recording sites, and the pattern of oscillation was not a simple alternation of long and short cycles. For instance, the

<table>
<thead>
<tr>
<th>Table of Abbreviations and Definitions</th>
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<tr>
<td>Coupling interval (Cl)—The time between consecutive extracellular electrograms at a specified site or between consecutive depolarizations in a transmembrane potential recording.</td>
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<tr>
<td>Cycle length—The same as coupling interval. Cycle length is used when referring to the sequence of intervals between activations at a particular site.</td>
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<tr>
<td>APD—Action potential duration measured at 90% repolarization. When action potential amplitude varied, the durations were measured at the voltage that corresponded to 90% repolarization for the largest action potentials.</td>
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<tr>
<td>Diastolic interval (DI)—The interval between the end of the preceding action potential and the next activation measured at the same voltage used to measure APD. Thus, DI + APD = C1 = CL.</td>
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C1, C2, C3—These identify consecutive cycles of reentrant activation after a stimulus that reset a tachycardia. Intervals are identified by reference to the cycle during which local activation (depolarization) occurred. Hence, for a given site, action potentials are identified as following local activation during a particular cycle, and DI and C1 are identified as preceding activation during a particular cycle.

T, T-1, T-2—These identify cycles of reentrant activation (depolarizations) preceding termination of a tachycardia. T refers to the cycle during which the tachycardia terminated because the impulse was blocked. T-1 is the next-to-last cycle. Interval-dependent conduction and interval-dependent changes in APD—These refer to changes in conduction velocity or APD that result from variations in the immediate preceding diastolic interval.

Stable tachycardia—One with less than 3 msec spontaneous variation between consecutive cycle lengths; unstable tachycardias had spontaneous variation of more than 3 msec.

Relative conduction velocity—The ratio of conduction velocity during an oscillation to the steady-state conduction velocity during a stable tachycardia for a particular region of the reentrant pathway. Thus, values less than one indicate relatively slow conduction.
sequence of cycle lengths after the stimulus, relative to the steady-state value of 298 msec, was shorter-shorter-longer-normal at site 1 and shorter-shorter-shorter-longer-shorter at site 7.

Cycle length oscillations resulted from changes in conduction velocity from beat to beat at one or more sites around the fixed reentrant pathway. Two dynamic tissue properties contributed to the sequence of conduction changes at a particular site during the oscillation. The first was interval-dependent conduction during the relative refractory period as described by the dependence of conduction velocity on the preceding DI. The second was changes in APD that also depended on the preceding DI; this relation has been called “electrical restitution.” Figures 2A and 2C demonstrate the correlations between DI and both conduction velocity and APD in the region of the microelectrode recording during the damped oscillation shown in Figure 1. Conduction was slower after shorter DIs because recovery of excitability was less complete.

The variations in APD influenced the oscillation because for any given CI they determined the local DI (DI = CI - APD). When changes in APD occurred during an oscillation, the changes in CI did not accurately reflect the changes in DI. The divergence between changes in CI and DI can be seen in the microelectrode recording in Figure 1 during C2, C3, and C4. For instance, during C3, local conduction was relatively slow (0.967) and the next APD was short (155 msec) after a short DI (119 msec) even though the CI (307 msec) was longer than normal. The discrepancy results from the long APD (188 msec) after C2. Thus, changes in APD explain the poor correlation between conduction velocity and the preceding CI during C2 and C3 in Figure 2B.

The preceding CI is a good predictor of conduction velocity only when the APD during that interval is constant so that CI and DI differ by a constant. This condition applies during the first cycle (C1) after a stimulus that resets a stable tachycardia because the previous APD has the steady-state value for the tachycardia cycle length. Figure 3 shows a smooth monotonic curve relating conduction velocity to CI for the first poststimulus cycle over an 80-msec range of CIs during a stable tachycardia. It also shows that this relation did not predict conduction velocity during cycles C2–C4 of a damped oscillation in the same experiment.

Alternation of effective refractory periods may occur in tachycardias with no cycle length oscillation. In two experiments with stable tachycardias, we observed a 15-msec range of coupling intervals during which premature stimuli would elicit a response during even-numbered cycles but not during odd-numbered cycles. The protocol involved stimuli delivered every 13th cycle.

Spontaneous Cycle Length Oscillations in Unstable Tachycardias

Unstable tachycardias had spontaneous oscillations of cycle length, DI, APD, and conduction.
DI-C4 period, large regression the stimulus. Points
labeled C1–C4 are data during the first four cycles after
the stimulus. Points labeled N represent data during the
normal stable tachycardia. Diagonal lines represent lin-
er regression of the five points in each graph. The
 correlations for each parameter with diastolic interval
 (Panels A and C) were better than with coupling interval
 (Panels B and D).

Usually the amplitude of the oscillation was irregu-
lar and did not involve a strict alternation of long
and short cycles. In the example shown in Figures 4
and 5, the oscillations were complex but not random;
the pattern repeated, with minor variation, every nine
cycles. The changes in DI and APD were much larger
than the changes in cycle length.

At a particular site, the changes in conduction
that contributed to spontaneous oscillations could
be explained by the dependence of both APD and
conduction time on the preceding DI just as was
shown above for damped oscillations in stable tachy-
cardias. Figure 6 shows that APD varied directly
and conduction time varied inversely with the pre-
ceding DI for one site during the oscillation shown
in Figures 4 and 5. Both correlations were signifi-
cant ($r = 0.99$ and $r = 0.91$, respectively; $p < 0.001$ for
both). Neither APD nor conduction time were cor-
related with the preceding cycle length because
cycle length did not parallel changes in DI. The
correlation coefficient between cycle length and DI
was 0.27, which was not significant ($p = 0.07$). The
poor correlation results from variations in APD
that, therefore, contribute to the oscillation by
influencing the next DI that determines local con-
duction during the next cycle.

Interval-dependent changes in APD can also per-
petuate oscillation of DI in the absence of cycle
length oscillations. For cycles 3–7 in Figures 4 and
5, local variations in conduction time were exactly
compensated by changes elsewhere in the circuit so
that cycle length was nearly constant. During this
period, large oscillations in DI at this site were
caused by alternations in APD.

Conclusions about the factors influencing conduc-
tion in Figures 4–6 are representative of other
experiments. We observed variations in APD in all
intracellular recordings during oscillation of reen-
trant tachycardias. Among seven microelectrode
impalings during reentry in four experiments,
the mean correlation coefficient for the relation
between APD and the preceding DI was $0.97 \pm 0.04$.
The slopes of the regression lines ranged from 0.57
to 0.96. The mean correlation coefficient for the
inverse relation between conduction time and DI
was $0.95 \pm 0.03$ for five impalings with large
enough changes in local conduction to measure the
differences accurately. The slopes of the regression
lines ranged from $-0.12$ to $-0.53$.

These data show that the changes in conduction
at one recording site were determined by the changes
in the local DI and the functions relating DI to APD
and conduction time. If conduction only varied at
that site, these functions totally determined the
pattern of cycle length oscillations. However, when
conduction varied at several sites in the circuit, as
in Figures 1, 4, and 7, the cycle length and DI at any
one site also depended on changes in conduction
time at other sites. During a given cycle, the local
DIs affecting conduction at different sites would not
be the same. The overall pattern of oscillation
resulted from the interaction of effects caused by
changes in APD and conduction time in different
parts of the circuit.

**Mechanism by Which Oscillations of Conduction,
Action Potential Duration, and Refractoriness
Cause Spontaneous Tachycardia Termination**

A specific pattern of DI oscillation appeared to be
responsible for most spontaneous terminations of
reentry in this model. The critical event was the
occurrence of a relatively long DI preceding the
next-to-last activation (T-1) near the site of block. This long interval had two effects that contributed to block; it prolonged APD and the duration of refractoriness near the site of block and it accelerated local conduction that contributed to shortening the last cycle length at the site of block. Figure 7A shows an example in which the transmembrane potential was recorded at a site just distal to the site where block occurred after a spontaneous oscillation of cycle length and APD. Both the longest DI (204 msec) and the longest cycle length during the recording period preceded the depolarization during T-1. As a result, the final action potential was longer (159 msec) and the conduction time between electrodes 6 and 5 was shorter than during any other cycle. Block can be attributed to the short final cycle at site 7 and the prolongation of refractoriness after T-1 in this region because of the long APD.

The importance of oscillations of APD and refractoriness in this mechanism of termination is shown by Figure 7B in which termination occurred when the last cycle was not as short as some earlier cycles. Block can be explained by a DI preceding T (95 msec) that was shorter than any previous DI. Because the last cycle length was not the shortest, the critical reduction of DI was dependent on the marked prolongation of APD after T-1 (195 msec).

Incidence of Spontaneous Termination of Reentry Caused by Oscillations Based on Extracellular Recordings Near the Site of Block

The role of oscillations of conduction and refractoriness in spontaneous terminations was analyzed with extracellular electrograms because transmembrane recordings near the site of block were not available for most observed terminations. Two patterns were considered evidence of oscillations contributing to termination. The first was a long-short sequence of cycle lengths during the last two cycles (T-1 and T) at the closest recording site proximal to the site of block. The second was a long-short sequence of conduction times during cycles T-2 and T-1 between the two closest recording sites proximal and distal to the site of block. The first pattern suggests that oscillations of conduction facilitated block by causing a short last cycle and that this occurred because of faster conduction after a long DI. The second pattern, specifically a short conduc-

**Figure 4.** Extracellular and intracellular recordings during spontaneous cycle length (CL) oscillations in an unstable tachycardia. Extracellular electrograms from 10 sites are shown with site 1 displayed at both the top and the bottom. A transmembrane potential recording near site 6 is shown at the bottom. The relative position and timing of the action potential upstrokes are indicated by dots near electrode 6. Large numbers between these dots indicate CL measured from the intracellular recording. The CL at sites 4 and 1 are also indicated. Conduction times between extracellular recording sites 4 and 1, 1 and 6, and 6 and 5 are shown along the diagonal lines indicating the spread of activation. An island of tissue around site 8 was damaged by the electrode. Early in the experiment, this site was activated in sequence between sites 9 and 7. Later, the electrogram amplitude decreased and, as seen in this recording, a relatively late and intermittent electrogram that did not reflect when the primary reentrant wave front activated this region of the circuit was visible at the damage site. The time line indicates 10- and 100-msec intervals.
tion time during T-1, indicates a long DI preceding T-1 because of the inverse relation between DI and conduction time. A short conduction time during T-1 is also an indirect indication of prolongation of APD after T-1 because both parameters depend on the preceding DI. For instance, for the data in Figure 6 there was a significant inverse correlation between conduction time and APD ($r=0.86$, $p<0.001$).

Ninety-nine episodes of spontaneous termination of reentry from 10 experiments were analyzed for the presence of these two patterns to determine whether oscillations of conduction and refractoriness caused the termination. The data are shown in Table 1. In 81 episodes, the patterns of oscillation of both CL and conduction times expected for this mechanism were observed. The data suggest that both oscillations of conduction and of refractoriness contributed to block in this group. Data from nine representative examples in this group are shown in Figure 8 and discussed more fully below.

The other 18 experiments did not show the expected long-short sequence of cycle length oscillation. In these experiments, oscillation of conduction did not contribute to termination by causing a short final cycle. Data from four representative examples are shown in Figure 9. However, in 11 of these cases (seven with constant cycle lengths and four with unexpected short-long cycle length oscillations), the pattern of conduction time oscillation at the site of block suggested that oscillation of DI and refractoriness contributed to the termination (see Figure 9, 3B and 3C). In those cases with unexpected cycle length oscillations ending in a short-long sequence, the prolongation of refractoriness after T-1 may have been sufficient to cause block despite the relatively long final cycle that would mitigate against it.

Thus, in 92 of 99 recordings, we found evidence suggesting that oscillation of DI and refractoriness with or without contributory cycle length oscillation contributed to spontaneous termination. Several factors may have contributed to the lack of such evidence in the other seven terminations. Five of these seven were from an experiment in which the signal from the electrode closest to the site of block was very noisy and not recorded. With marked variations in conduction in this region our closest proximal recording electrode may not have been close enough to reflect the sequence of cycle lengths at the site of block. Three recordings from this

**FIGURE 5.** The pattern of spontaneous oscillations at the intracellular recording site shown in Figure 4. Oscillations of action potential duration (APD), conduction time, diastolic interval (DI), and cycle length (CL) are shown for 56 cycles of the unstable tachycardia. Conduction time was measured between recording sites 6 and 5 in the immediate vicinity of the action potential recording. For each cycle, the APD and conduction time are aligned with the immediately preceding diastolic interval and cycle length. The oscillations of diastolic interval are much larger and not directly correlated with the oscillations of cycle length. APD is related directly and conduction time inversely to changes in DI. The 11 cycles shown in Figure 4 are indicated by the bar in the bottom left. Measurements are in msecs and the time scales are identical except for conduction time, which is increased twofold.

**FIGURE 6.** Plots relating local conduction time and action potential duration (APD) to preceding diastolic interval and cycle length at the intracellular recording site shown in Figure 4. The data are the same as that shown during the time sequence in Figure 5. Both conduction time and APD were closely correlated to the preceding diastolic interval (Panels A and C) and poorly correlated with preceding cycle length (Panels B and D).
experiment (including Figure 9, 4A and 4B) and one of the other two recordings showed increasing cycle lengths and local conduction times just before the termination, suggesting that progressive depression of excitability or prolongation of refractoriness may have caused block. In the other recording, block occurred in a region with relatively slow conduction, but there were no clues to explain why block occurred.

The examples of oscillatory termination shown in Figure 8 illustrate several points. Although all examples terminate with a long-short sequence of cycle lengths, the long cycle length preceding T-1 was not always the longest cycle length and the short cycle preceding T was not always the shortest. However, whenever the final cycle was not the shortest, the conduction time during T-1 was the shortest conduction time, which indirectly indicates that the DI preceding T-1 and the APD after T-1 were exceptionally long. This pattern indicates the critical contribution of oscillation of APD and refractoriness to termination of reentry.

Occasionally, the oscillation during the last 10 cycles was a strict alternation of long and short cycles (Figure 8, 2A). In these cases, the beat-to-beat variations in conduction velocity occurred at only one part of the circuit, and that was the site

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**Figure 7.** Spontaneous terminations of two episodes of reentry from the same experiment. Panel A shows an action potential recording just distal to the site of block and extracellular electrograms recorded from 10 sites around the ring. The transmembrane potential at the bottom was recorded near site 6 as indicated by the dots. Cycle lengths (CLs) measured at sites 5, 6, 7, and 1 are shown. Conduction times between sites 5 and 1, 1 and 7, 7 and 6, and 6 and 5 are also shown. The CLs preceding T-1 at sites 7 and 6 were the longest that occurred (343 and 337 msec). The action potential duration (APD) after T-1 and the preceding diastolic interval (DI) are also the longest that were observed. At site 7, proximal to the site of block, the last two CLs had a long-short sequence. Linear regression between preceding DI and APD at the intracellular recording site had a correlation coefficient of 0.98 and a slope of 0.57. The relation between conduction time from site 6 to site 5 and the preceding DI had a correlation coefficient of 0.96 and a slope of -0.53. The time lines indicate 10- and 100-msec intervals. As in Figure 4, the electrogram at the damaged site 8 occurred late relative to when the reentrant wavefront passed this part of the circuit. Panel B shows only a transmembrane potential recorded proximal to the site of block during another termination. The recording is from the same impalement shown in Figure 4. The last low amplitude action potential, recorded just before the reentrant impulse blocked, did not follow an exceptionally short CL (290 msec). However, the CL (304 msec) and DI (145 msec) preceding T-1 were exceptionally long and were followed by an exceptionally long APD (195 msec) that shortened the last DI. The time scale is the same as for Panel A.
TABLE 1. Patterns of Oscillation of Cycle Length and Conduction Times During Spontaneous Termination of Reentry

<table>
<thead>
<tr>
<th>Cycle length oscillation during T-1 and T</th>
<th>Long-short conduction time during T-2 and T-1</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-short</td>
<td></td>
<td>81</td>
<td>0</td>
<td>81</td>
</tr>
<tr>
<td>No change</td>
<td></td>
<td>7</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Short-long</td>
<td></td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>92</td>
<td>7</td>
<td>99</td>
</tr>
</tbody>
</table>

where block occurred. The figure shows that the local changes in conduction time were very similar to the variations in cycle length.

More commonly, the cycle length oscillations were irregular, and variations in conduction occurred in more than one part of the circuit. For instance, in Figure 8 (5A, 7A, 7B, and 10A), the local changes in conduction time accounted for only part of the cycle length oscillation. On the other hand, in 3A, variations in local conduction times were larger than the changes in cycle length because of opposing compensatory changes in conduction in other parts of the ring. Complex oscillations were always associated with variation in conduction at more than one site in the circuit.

Figure 8 also shows that the pattern of the oscillations preceding termination varied considerably among experiments as well as among recordings from the same experiment. In several oscillatory terminations (5A, 7A, 7B, and 10A), a three-cycle periodicity (short-long-intermediate-short) occurred before the final two or four beats with alternating long and short cycles. Thus, although the pattern during the last two cycles was similar in all these examples, the previous patterns of oscillation leading to the conditions for termination were complex and variable.

We also observed a specific pattern of alternation in the amplitude or duration of electrograms during the cycles preceding termination near the site of block during 52 of 99 terminations. A lower amplitude or longer duration electrogram was interpreted as indicating that the impulse encountered more refractory tissue. The pattern is illustrated in Figure 7 at site 7 where the electrogram amplitude was larger during T-1 and smaller during T-2 and T. This pattern further supports the role of oscillations of conduction and refractoriness in tachycardia termination.

Discussion

Tachycardias in this preparation involve reentry around a fixed path with incomplete recovery of excitability. Incomplete recovery of excitability is demonstrated by slower conduction of premature impulses that reset the tachycardia even slightly. These characteristics also apply to the model of atrial flutter in chronically instrumented animals and isolated heart preparations from which the in vitro model was derived.

The present study shows that cycle length oscillations may be observed in this type of reentry in either stable or unstable tachycardias. However, stable tachycardias exhibit damped oscillations when perturbed by premature stimuli, whereas unstable tachycardias demonstrated spontaneous cycle length oscillations that sometimes lead to spontaneous termination of the tachycardia. Two dynamic tissue properties, interval-dependent conduction and interval-dependent changes in APD (electrical restitution), were sufficient to explain the local changes in conduction that contribute to the oscillations and the mechanism by which oscillations caused termination. The changes in both conduction and APD
were adequately predicted by changes in the preceding DI and were poorly predicted by the entire preceding CI when large changes in APD occurred. These reentrant circuits acted as feedback systems in which changes in the duration of one cycle caused changes in conduction that altered subsequent cycles. Simson et al. used the concept of a feedback system driven by interval-dependent conduction to explain the difference between stable and unstable tachycardias in both biological (canine) and computer models simulating atrioventricular reentry with an accessory bypass tract as in the Wolff-Parkinson-White syndrome. In that reentrant circuit, only the atrioventricular node demonstrated interval-dependent conduction at the tachycardia cycle length. The stability of the tachycardia was determined by the magnitude of interval-dependent change in conduction as indicated by the slope of the atrioventricular nodal conduction curve. A slope steeper than −1 indicated that cycle length would oscillate with progressively increasing alternations of long and short cycles until a sufficiently short cycle caused block. An essential characteristic of that model was that one source of feedback (interval-dependent conduction), operating at only one site in the circuit, led to a regular alternation of long and short cycles that progressively either decreased or increased in amplitude.

The oscillation in the experiments reported here involve a more complex feedback system because variations in conduction usually occurred at more than one site and because two dynamic tissue properties were involved. A strict alternation of long and short cycle lengths was seen in some experiments in which variations in conduction velocity were limited to one part of the circuit. However, more irregular and complex oscillations occurred when conduction velocity varied at more than one site in the circuit.

The interaction between interval-dependent conduction and changes in APD in the feedback that drives the oscillation could be best described in terms of how a perturbation of one DI affected the DI during the next cycle. For instance, a long DI during one cycle would cause faster conduction of the impulse (which would tend to shorten the next cycle length) but also would prolong the next APD. Both factors would reduce the duration of the next DI and slow conduction of the impulse that followed it.

Because changes in APD contributed to the oscillations, the slope of the restitution curve over the range of DIs observed during the oscillation should influence the magnitude of the oscillations and, therefore, the stability of the tachycardia. This slope indicates how much a given perturbation of one DI will alter the next DI due to the change in APD. Changes in APD should increase the tendency to oscillate when the slope is positive. A steep slope should favor larger unstable oscillations. It is noteworthy that the slope of the restitution curve for the stable tachycardia in Figure 2A was 0.66, whereas the slope of the restitution curve for the unstable tachycardia in Figure 6A was 0.96.

The changes in APD we observed in this preparation are characteristic of atrial and ventricular muscle. Action potential alternans can occur in atrial or ventricular muscle during rapid pacing at a constant cycle length at which the slope of the electrical restitution curve is very steep. Oscillations of refractoriness have also been observed in the human His-Purkinje system and ventricular muscle at short pacing cycle lengths. Action potential alternans represents a persistent oscillation of DI due to interval-dependent changes in APD. It indicates that significant variations in APD can occur in these tissues under conditions that may be relevant to reentrant tachycardias.

Oscillations of APD and refractoriness may sometimes occur and cause termination of reentry without contributory cycle length oscillation. In this preparation, we observed alternation of refractory periods in two stable tachycardias, and we previously reported action potential alternans during reentry. Figures 4 and 5 show a period of action potential alternans in an unstable tachycardia when the cycle length was nearly constant. Finally, there were several terminations that appeared to result from oscillations of refractoriness when the sequence of cycle lengths did not favor termination (Table 1 and Figure 9). We predict that tachycardias in circuits with little interval-dependent conduction

![Figure 9](http://circ.ahajournals.org/)
might terminate due to oscillations of refractoriness when no cycle length oscillations are present.

We found an excellent correlation between APD and the immediate preceding DI during spontaneous or induced oscillations. Electrical restitution curves are usually constructed by plotting the APD at various coupling intervals after pacing at a constant cycle length. However, after abrupt changes in pacing cycle length, there is slow adaptation of APD that requires many cycles. Under such conditions, APD is not determined solely by the preceding diastolic interval. Apparently, these slowly changing factors influencing APD are not significant when the cycle length is oscillating above and below a mean tachycardia cycle length.

It was surprising that the curve relating APD to DI during spontaneous oscillations appeared linear when most studies have described electrical restitution curves as a sum of exponential functions. This reflects the limited range of DIs observed during the oscillations. At longer DIs, the slope of the curve would be expected to decrease.

The concept of wavelength that represents the spatial extent of refractory tissue for a propagating impulse has been used to predict effects of drugs on reentrant arrhythmias. The wavelength equals the product of conduction velocity and the duration of refractoriness. A tachycardia cannot exist if the wavelength exceeds the length of the reentrant circuit. Factors that shorten the wavelength tend to facilitate reentry, and factors that prolong it may favor termination caused by block due to refactoriness. This concept is useful but has limitations with respect to terminations caused by oscillation. First, during cycle length oscillations, both conduction velocity and the refractory period are constantly changing. Block results from a transient increase in both conduction velocity and refractoriness during the last cycle. One could say that the wavelength during the last cycle transiently exceeded the length of the circuit even though the "steady-state" wavelength at the mean cycle length of the tachycardia did not. Second, measurements of the wavelength at a constant cycle length fail to consider factors that influence the magnitude of the oscillations, such as the slope of conduction and the restitution curves.

Cycle length oscillations occur in this model because the reentrant impulse propagates through partially refractory tissue. Cycle length oscillation would not be expected in reentry around a fixed path with complete recovery between depolarizations. The duration of the relative refractory period and the magnitude of interval-dependent conduction changes are greater in normal atrial muscle than in normal ventricular muscle, perhaps in large part because the terminal phase of repolarization is more gradual. However, ischemic or infarcted canine and human ventricular muscle and Purkinje tissue have prolonged relative refractory periods and show marked interval-dependent conduction changes.

Furthermore, responses to resetting of human ventricular tachycardia indicate that there is significant interval-dependent conduction in the reentrant circuit.

In the tricuspid ring preparation, cycle length oscillations result entirely from changes in conduction velocity. In other reentrant circuits, changes in the path length may also contribute. However, regardless of the mechanism, cycle length oscillations may still cause oscillations of refractoriness that terminate the tachycardia. Oscillations of conduction may be particularly likely in leading circle reentry because the excitable gap must be short in at least part of the circuit during tachycardia.

Cycle length oscillations have been observed preceding termination of reentry in experimental models of ventricular tachycardia and in patients with atrioventricular tachycardias with an accessory bypass tract and atrioventricular nodal reentry. We have frequently observed complex cycle length oscillations before termination of nonsustained ventricular tachycardia recorded during ambulatory monitoring (unpublished observations). We suspect that cycle length oscillations may contribute to termination in many experimental and clinical tachycardias caused by reentry. However, proving or excluding a role for oscillations in terminating clinical arrhythmias may be difficult when recording outside the circuit because the typical pattern of cycle length oscillation we observed at the site of block was often not present in other parts of the circuit.

The present study illustrates mechanisms for tachycardia termination caused by oscillations of conduction and refractoriness that have not been fully appreciated. It also relates the occurrence of oscillations to electrophysiological characteristics of the circuit that may be present in some clinical tachycardias. The presence of cycle length oscillations either spontaneously or after premature stimulation may indicate how stable a tachycardia is and identify characteristics useful for selecting drug therapy.

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L H Frame and M B Simson

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